IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Salvatore AVOLIO et al.	Art Unit: 1624
Serial No.:	10/500,971	Examiner: Deepak R. RAO
Filed:	February 16, 2005	Case No.: ITT0039YP USA
For:	PYRIMIDINONE VIRAL POLYMERASE INHIBITORS	

DECLARATION UNDER 37 C.F.R. §1.132

I, Michael Rowley, a citizen of the United Kingdom, hereby declare and state:

1. I have a doctoral degree in Natural Sciences, which was conferred upon me by the Faculty of the University of Cambridge in Cambridge, England, in 1986. My thesis was entitled "Some Uses of Tin Compounds in Organic Synthesis."

2. I was a post-doctoral research fellow at Harvard University from 1986 to 1988, and concentrated my research during this period on the total synthesis of Ophiobolin C, under the direction of Professor Yoshito Kishi.

3. I have been employed by Merck & Co., Inc., or subsidiaries thereof, since September of 1988, and I have had a total of 27 years of work and research experience in organic synthesis and the development and synthesis of pharmaceutically active agents.

4. I am an active member of the Royal Society of Chemistry, the Italian Chemical Society and the American Chemical Society.

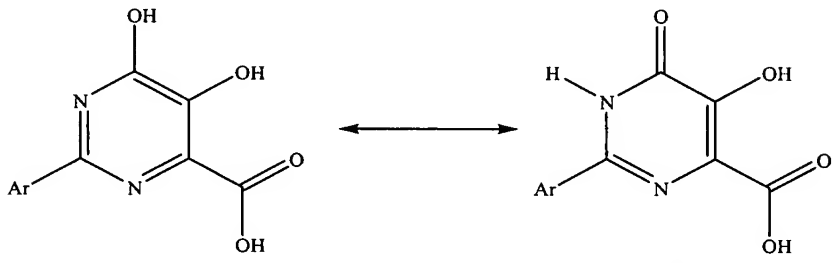
5. A representative listing of publications of which I am an author is provided as Annex A to this Declaration.

6. A representative listing of patents and published patent applications on which I am a named inventor is provided as Annex B to this Declaration.

7. I have reviewed the above-captioned patent application and the currently pending claims, as well as the proposed claim amendments.

8. I have reviewed the outstanding Final Rejection, particularly the rejection of claims 1, 3-9, 11, 13 and 14 under 35 U.S.C. §103(a) over International Patent Application Publication No. WO 02/006246 to Gardelli et al. I have also reviewed the Gardelli reference.

9. The '246 publication teaches 2-aryl-4,5-dihydroxy-6-carboxypyrimidines of formula I that exist in equilibrium with tautomeric forms such as those of formula IA. *See* '246 publication, page 1, line 25 – page 2, line 12.



I IA

10. The cited '246 publication teaches that compounds of its formula I are tautomeric; that is, the compounds of the '246 publication undergo tautomeric rearrangements in which hydrogen from a ring enol moves to the adjacent nitrogen and

back. These tautomeric forms exist because the ring nitrogens are unsubstituted. Such chemical rearrangements are well understood in the arts relating to organic chemistry and chemical synthesis.

11. When the nitrogen has an alkyl substitutent, as in R^1 of the claimed compounds, the compounds cease to exist as tautomers. That is, the tautomeric rearrangement is no longer possible; the "blockage" of tautomeric rearrangement by substitution is also well known.

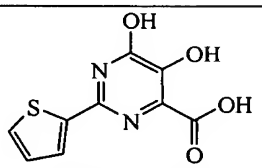
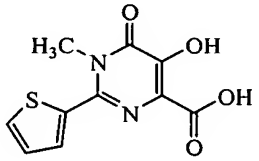
12. The '246 publication does not suggest blocking tautomerization by providing an alkyl substituent on the ring nitrogen, as in the pending claims. Rather, the '246 publication specifically discloses compounds that form tautomers.

13. However, further research showed that alkyl substitutions of the ring nitrogen, as currently claimed, not only provide distinct compounds that do not undergo tautomeric rearrangements, but that have improved oral bioavailability. Such improved oral bioavailability over the tautomeric compounds disclosed and claimed in the '246 publication would not have been understood from the disclosures of the '246 publication, at least because there is no indication in the reference that blocking tautomerization would provide such improved compounds.

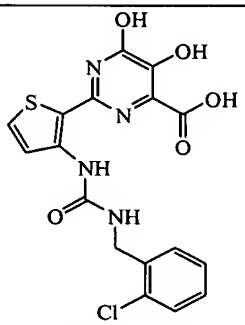
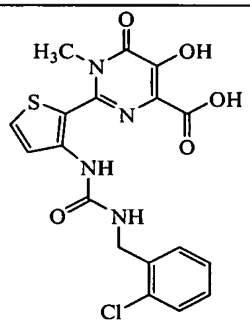
14. I and/or those under my direct supervision and control have prepared and tested several representative compounds according to the claims and corresponding tautomeric compounds. Comparative data for representative compounds is provided in the tables below and discussed in the following paragraphs. In the tables, the term "F(rat)%" refers to the percentage of compound that was found to be orally

bioavailable in rats, as determined by dosing the compound orally and intravenously to rats, measuring the concentration at various time points, and calculating the Area Under the concentration-time Curve (AUC). The oral bioavailability is defined as the ratio of the AUC when dosed orally to the AUC when dosed intravenously. The term "IC_{50}" refers to the concentration of the compound required to inhibit, in a biochemical reaction *in vitro*, fifty percent of the activity of the HCV NS5B RNA-dependent RNA polymerase activity.

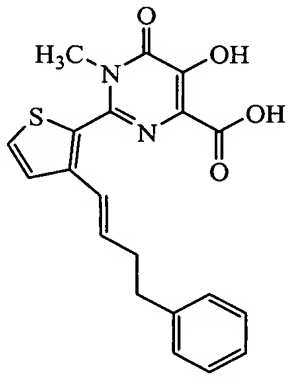
15. Table 1

Compound	 (tautomeric)	
F(rat)%	6	25
IC_{50} (μM)	2.5	4.7

16. Table 2

Compound	 (tautomeric)	
F(rat)%	1	12
IC_{50} (μM)	0.16	1.2

17. In addition, the following compound was found to have an IC_{50} of 8.2 μM and an F(rat)% oral bioavailability of 100%.



18. As can be seen from the compounds tested, tautomeric compounds such as those disclosed in the '246 publication do not provide the oral bioavailability achieved by the alkyl substituted compounds of the claims. To provide effective therapy for HCV, it is preferable to have compounds that are orally bioavailable, and thus, the compounds of the claims show potential, unexpected, advantage.

19. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application and/or of any patent issuing therefrom.

Date: 18 September 2007

Michael Rowley

Annex A: Representative Publications

1. Jones, P.; Altamura, S.; Chakravarty, P. K.; Cecchetti, O.; De Francesco, R.; Gallinari, P.; Ingenito, R.; Meinke, P. T.; Petrocchi, A.; Rowley, M.; Scarpelli, R.; Serafini, S.; Steinkuehler, C., *A series of novel, potent, and selective histone deacetylase inhibitors*, 16 BIOORG. MED. CHEM. LETT. 5948-52 (2006).

2. Summa, V.; Petrocchi, A.; Matassa, V. G.; Gardelli, C.; Muraglia, E.; Rowley, M.; Paz, O. G.; Laufer, R.; Monteagudo, E.; Pace, P., *4,5-Dihydroxypyrimidine Carboxamides and N-Alkyl-5-hydroxypyrimidinone Carboxamides Are Potent, Selective HIV Integrase Inhibitors with Good Pharmacokinetic Profiles in Preclinical Species*, 49 J. MED. CHEM. 6646-49 (2006).

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13. Gibson, K.R.; Thomas, S. R.; Rowley, M., *An intramolecular sulfoxide alkylation-elimination approach to the [1,2,3]triazolo[1,5-a]pyrimidine ring system*, (5) SYN. LETT. 712-714 (2001).

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15. Rowley, M.; Bristow, L.; Hutson, P., *Perspective: Current and novel approaches to the drug treatment of schizophrenia*, 44 J. MED. CHEM. 477-501 (2001).

16. Crawforth, J.; Goodacre, S.; Maxey,R.; Bourrain, S.; Patel, S.; Marwood, R.; O'Connor, D.; Herbert, R.; Hutson, P.; Rowley, M., *3-(4-Piperidinyl)- and 3-(8-aza-bicyclo[3.2.1]oct-3-yl)-2-phenyl-1H-indoles as bioavailable h5-HT_{2A} antagonists*, __ BIOORG. MED. CHEM. LETT. 2701-03 (2000).

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high affinity agonists of human GABA-A receptors containing the α1 subunit, 10 BIOORG. MED. CHEM. LETT. 1381-84 (2000).

19. Ahmed, A.; Clayden, J.; Rowley, M., *1,3,4,5-Tetrahydroazepin-2-ones by dearomatising anionic cyclisation of N-allyl-1-naphthamides*, 12 SYN. LETT. 1954-56 (1999).

20. van Niel, M. B.; Collins, I.; Beer, M. S.; Broughton, H. B.; Cheng, S. K. F.; Goodacre, S. C.; Heald, A.; Locker, K. L.; MacLeod, A. M.; Morrison, D.; Moyes, C. R.; O'Connor, D.; Pike, A.; Rowley, M.; Russell, M. G. N.; Sohal, B.; Stanton, J. A.; Thomas, S.; Verrier, H.; Watt, A. P.; Castro, J. L., *Fluorination of 3-(3-(Piperidin-1-yl)propyl)indoles and 3-(3-(1-piperazinyl)propyl)indoles Gives Selective Human 5-HT_{1D} Receptor Ligands with Improved Pharmacokinetic Profiles*, 42 J. MED. CHEM. 2087-2104 (1999).

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45. Stevenson, G.I.; Leeson, P.D.; Rowley, M.; Sanderson, I.; Stansfield, I, *Synthesis of* cis *and* trans *4-Amido 2-Carboxytetrahydroquinolines, high affinity ligands at the glycine site of the NMDA Receptor*, 2 BIOORG. MED. CHEM. LETT. 371 (1992).

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Annex B: Representative Patents and Patent Publications

1. Dioxotetrahydroquinolines. EP 0459561 A (1991).

2. Hydroxyquinolone derivatives. EP 0481676 A (1992).

3. 2(1H)-Quinolone Derivatives. WO 9310783 A (1993).

4. 3-Phenyl-2(1H)-quinolone derivatives. WO 9311115 A (1993).

5. (Piperidinyl)pyrazoles and Analogs. WO 9410145 A (1994).

6. Dopamine receptor subtype ligands. WO 9410162 A (1994).

7. Pyrimidine derivatives for treatment of dopamine disorders. WO 9426733 A (1994).

8. Fused tricyclic heteroaromatic derivatives. WO 9507893 A (1995).

9. Fused tricyclic heteroaromatic derivatives. WO 9507262 A (1995).

10. Piperazine, piperidine and tetrahydropyridine derivatives. WO 9718203 (1997).

11. Substituted piperidine derivatives as selective agonists of 5-HT receptors. WO 9718202 (1997).

12. Indolylalkyl piperazines as selective 5-HT1 agonists. WO 9719943 (1997).

13. Preparation of heteroarylpyridones as GABAA $\alpha 2/\alpha 3$ ligands. WO 9855480 (1998).

14. Preparation of phenylindoles as 5-HT2A receptor ligands. WO 9911619 (1999).

15. Preparation of 3-(piperidin-4-yl)-2-phenylindoles as 5-HT2A receptor antagonists. WO 9911641 (1999).

16. Preparation of 3-(piperidin-3-yl)-1H-indole derivatives as 5-HT2A receptor antagonists for treatment of psychotic disorders such as schizophrenia. WO 9947511 (1999).

17. Preparation of triazolopyrimidines as ligands for GABA receptors. WO 9965907 (1999).

18. Preparation of 3-azabicyclooctyl-2-phenylindoles as selective antagonists of 5-HT2A receptors. WO 0004017 (2000).

19. Preparation of phenylindoles as 5-HT2A receptor ligands. WO 0005229 (2000).

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